CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Imazamox

Chemical Code # 5757, Tolerance # 52849

10/24/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 174835 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: tCRR183086N
Corlett and Eya, 10/24/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

042; 174807; "Chronic Dietary Toxicity and Oncogenicity Study with AC 299,263 in the Albino Rat"; (Fischer, J.E., Hess, F.G.; Experimental Pathology Laboratories, Inc., Herndon, VA., and American Cyanamid Co., Princeton, NJ.; Study No. T-0496; 06/20/95). Charles River CD® Sprague Dawley derived rats (65 rats/sex/group) were fed AC 299,263 (Lot # AC 6935-63; 97.1% a.i.; diet adjusted to a.i. content of 98.2% based on previous analyses) in the diet at concentrations of 0, 1000, 10,000, 20,000 ppm ((M): 0, 52, 528, 1068 mg/kg/day, (F): 0, 63, 626, 1284 mg/kg/day, respectively) for 24 consecutive months. There were no changes in clinical signs of toxicity, ophthalmology, food consumption values, body weight gain, hematology, clinical chemistry, urinalysis parameters, absolute or relative organ weights, or microscopic changes observed during the study that could be attributed to administration of the test material. Survival was unaffected by the administration. **No adverse effect indicated. Chronic NOEL (M/F): 20,000 ppm (M: 1068 mg/kg/day, F: 1284 mg/kg/day) (based on lack of observable effects at concentrations up to 20,000 ppm); **Study acceptable.** (Eya, 07/10/00).

CHRONIC TOXICITY, RAT

See Combined, Rat

CHRONIC TOXICITY, DOG

043; 174808; "One-Year Dietary Toxicity Study with AC 299,263 in Purebred Beagle Dogs"; (Kelly, C.M.; Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ 08875-2360.; Study No. 93-3154; 05/25/95). Thirty Beagle dogs (5/sex/group) were fed AC 299,263 (Lot # AC 6935-63; 97.1% a.i.) in the diet at concentrations of 0, 1000, 10,000, 40,000 ppm ((M): 0, 29, 283, 1174 mg/kg/day, (F): 0, 30, 282, 1156 mg/kg/day, respectively) for at least 1 year. None of the parameters evaluated in this study, including mortality, body weights, food consumption, physical observations, hematology, clinical chemistry, ophthalmology, organ weight data, and macroscopic and microscopic examinations revealed any treatment-related effects due to administration of test material. There were no histopathological effects associated with dietary administration of AC 299,263 to dogs at the dose levels and the duration tested. **No adverse effect indicated. Chronic NOEL (M/F): 40,000 ppm (M: 1174 mg/kg/day, F: 1156 mg/kg/day) (based on lack of observable treatment-related effects at concentrations up to 40,000 ppm); **Study acceptable.** (Eya, 07/14/00).

ONCOGENICITY, RAT

See Combined, Rat

ONCOGENICITY, MOUSE

**044; 174809; "An Oncogenicity Study with AC 299,263 in Mice"; (Kelly, C.M.; Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ 08875-2360.; Study No. 92-2164; 06/12/95). Three hundred thirty CD®-1 mice (55/sex/group) were fed AC 299,263 (Lot # AC 6935-63; 97.1% a.i., see p. 280) in the diet at concentrations of 0, 500, 3500, 7000 ppm ((M): 0, 73, 535, 1053 mg/kg/day, (F): 0, 96, 664, 1348 mg/kg/day, respectively) for at least 18 months. None of the parameters evaluated in this study, including mortality, body weights, food consumption, physical observations, hematology, organ weight data, and macroscopic and microscopic examinations revealed any adverse effects due to administration of test material. There were no carcinogenic effects or other findings of toxicological significance associated with dietary administration of AC 299,263 to mice at the dose levels and the

duration tested. **No adverse effect indicated. Chronic NOEL (M/F):** 7000 ppm (M: 1053 mg/kg/day, F: 1348 mg/kg/day) (based on lack of observable effects at concentrations up to 7000 ppm); **Study acceptable.** (Eya, 07/20/00).

REPRODUCTION, RAT

** 047; 174813; "A Two-Generation Reproduction Study with AC 299,263 in Rats"; (Schroeder, R.E.; Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ.; Laboratory Project Study No. 92-4043; 05/26/95); Thirty rats/sex/group (P1) and (F1) were dosed orally in the diet with 0, 1000, 10,000 and 20,000 ppm of AC 299,263 (Lot # AC 6935-63, 97.1% purity, test diet adjusted for content of a.i. according to the original analysis of 98.2%) for two generations. The treatment periods included 10 weeks prior to mating for P1 and 11 weeks prior to mating for F1 generation, and treatment continued during a 20-day mating period and post-mating interval until sacrifice. Mated females continued to be treated during the gestation, lactation and post-weaning periods until sacrifice. No treatment-related effects with AC 299,263 at a dietary level up to 20,000 ppm were evident from the evaluation of parental or neonatal parameters as well as reproductive performance. The only parental effect observed was reduction (-11.3%) in mean weight gain in F1-females over 11-week pre-mating period, which was statistically significant without any dose response relationship. **No adverse effect indicated. Parental Systemic NOEL: 20,000 ppm** ((M) P1: 1554, F1: 1469 mg/kg/day; (F) P1: 1826, F1: 1705 mg/kg/day); **Reproductive NOEL: 20,000 ppm** (ca. 1639 mg/kg/day, due to lack of treatment-related effect at HDT); **Developmental NOEL: 20,000 ppm** (ca. 1639 mg/kg/day, due to lack of adverse effects on the neonatal parameters). **Study acceptable.** (Eya, 08/10/00).

TERATOLOGY, RAT

** 045; 174810; "An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Study with AC 299,263 in Rats" (Foss, J.A.; Argus Research Laboratories, Inc., Horsham, PA; Study No: 101-020; Sponsor's Study No.: 971-93-105, 03/29/94). Twenty five Crl:CD®BR VAF/Plus® (Sprague-Dawley) presumed pregnant rats were treated by oral gavage once daily with 0, 100, 500, or 1000 mg/kg/day of AC 299,263 (Lot # AC 6935-63, 97.1 % purity, adjusted for content of a.i. according to the previous analysis result, i.e., 98.2%) from day 6-15 of presumed gestation. No deaths, abortions, or premature deliveries occurred during the study. All clinical observations were considered to be unrelated to the treatment, and no gross lesions were identified at necropsy. Body weight gains during the dosing period (days 6-12 of gestation), and feed consumption (absolute and relative) during the dosing period (days 6-16 of gestation) were reduced in the 1000 mg/kg/day group. However, the body weight gains were comparable in all groups during the post-dosage period (days 16-20 of gestation). No fetal malformations or variations were caused by the administration of the test material. Only one fetus in the high dose group had skeletal malformations (short, broad, bent ribs), which were considered unrelated to the administration of AC 299,263. **No adverse effects. Maternal NOEL:** 500 mg/kg/day (based on minimal reduction of body weight gain and absolute and relative feed consumption value at 1000 mg/kg/day); **Developmental NOEL:** $\geq$ 1000 mg/kg/day (based on no test material related malformation). **Study acceptable.** (Eya, 07/28/00)

TERATOLOGY, RABBIT

** 046; 174811; "An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Definitive Study with AC 299,263 in Rabbits" (Hoberman, A.M.; Argus Research Laboratories, Inc., Horsham, PA; Study No: 101-021; Sponsor's Study No.: 971-93-107, 05/10/95). Twenty New Zealand White [Hra:(NZW)SPF] presumed pregnant rabbits were treated by oral gavage once daily with 0, 300, 600, or 900 mg/kg/day of AC 299,263 (Lot # AC 6935-63, 97.1 % purity, adjusted for content of a.i.) from day 7-19 of presumed gestation. Biologically important changes occurred in the groups treated at 600 and 900 mg/kg/day, in the relative feed consumption which were significantly reduced during days 7-20 of gestation, and in the absolute and relative feed consumption values on days 7-29 of gestation. The pattern

of effect increased as dosing continued during the gestation period in these 2 higher dose levels. There was a 19% reduction of the maternal body weight gain in 900 mg/kg/day group during the dosing period, and the weight gain remained depressed (ca. 21%) during the post-treatment period. A doe from the 900 mg/kg/day group prematurely delivered on day 29 of gestation, with persistent weight loss and reduced feed consumption after day 11 of gestation. Caesarean sectioning and litter parameters were unaffected by the treatment. No gross external, soft tissue or skeletal malformations or variations in the fetuses were considered due to treatment. Analyses of the average number of fetal ossification sites per litter did not reveal any differences among the 4 dose groups. **No adverse effects. Maternal NOEL:** 300 mg/kg/day (based on reduced feed consumption at 600 and 900 mg/kg/day and reduced weight gain at 900 mg/kg/day); **Developmental NOEL:** 900 mg/kg/day (based on the absence of treatment-related effects at HDT); **Study acceptable.** (Eya, 08/02/00).

GENE MUTATION

048; 174825; "Evaluation of CL 299,263 in a Bacterial/Microsome Mutagenicity Assay" (Mulligan, E., American Cyanamid Company, Agricultural Products Research Division, Princeton, NJ., Study No.: 92-02-001, 02/24/94). The test article, CL 299,263 (Batch No: AC6935-63; 98.2% purity; test solutions were prepared unadjusted for the purity) was tested in the bacterial reverse mutation assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *E. coli* strain WP2 *uvr*A in the presence and absence of Aroclor-induced rat liver S9. The tester strains were treated at 5-dose levels of test material ranging from 100 to 5000 ug/plate with and w/o activation (48 hours incubation at 37 ^{o}C). Each treatment level was plated in triplicate. The assay was conducted twice to confirm the results. There were no reproducibly significant increases in revertants at any dose level in any strain. CL 299,263 did not induce either base-pair or frame-shift mutations in any of the tester strains in bacteria, at doses up to 5000 ug/plate with or without added metabolic activation. **No adverse effect indicated. Study Acceptable. (Eya, 08/16/00).

048; 174827; "Evaluation of CL 299,263 in the Mammalian Cell CHO/HGPRT Mutagenicity Assay" (Sharma, R.K.; Genetic Toxicology Lab, American Cyanamid Company, Agricultural Research Division, Princeton, NJ, Study No. 92-05-001, 06/01/93). Chinese hamster ovary cells for the CHO/HGPRT mutation assay were treated for 5 hours at 37 $\pm$ 2 ^{o}C with CL 299,263 (Lot # AC6935-63, 98.2% purity, unadjusted for content of a.i.) at concentrations of test material ranging from 50 to 4000 ug/mL. The assays were performed with and w/out metabolic activation in 4 trials (2 trials each). Duplicate cultures were prepared for each treatment level. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. The test material did not induce mutations at the HGPRT locus in CHO cells at doses up to and including 4000 ug/mL. **No adverse effect indicated. Study Acceptable. (Eya, 08/18/00).

CHROMOSOME EFFECTS

048; 174829; "AC299,263: Test for Chemical Induction of Chromosome Aberration in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation"** (Kumaroo, P.V., SITEK Research Lab., Rockville, MD., SITEK Study No.:0256-3114, 02/16/94). Four replicate cultures at each dose were treated in medium containing 10% fetal bovine serum without S9 or in serum free medium with S9, and 0, 417, 833, 1667 and 3333 ug/mL of AC299,263 (Lot # AC6935-63; purity: 97.1%, with dose level unadjusted for purity (p. 82). Chromosome aberrations were scored from cells treated at 833, 1667 and 3333 ug/mL (solubility limit in the activated system). One hundred metaphases were scored from each of the two replicate cultures at each dose level at each harvest time (13 and 48 hours, -S9; 19 and 48 hours, +S9). The maximum reduction in mitotic index (toxicity determination) observed at 3333 ug/mL at 13 and 48 hour harvest were 11 and 38%, respectively, without S9. In the activated system with S9, the maximum reduction was 58% (19 hours) and 27% (48 hours), and the non-activated control of the activated system was 17% (19 hours). A confirmatory assay was conducted with harvest time of 13 and 24 hours ($\pm$S9). AC299,263 was evaluated to be non-clastogenic in the *in vitro* Chromosomal

Aberration assay. **No adverse effect indicated. Study Acceptable** (No statistically significant increase was observed in the number of cells with aberrations at any of the dose levels with or without S9 activation) (Eya, 08/28/00).

DNA DAMAGE

048; 174828; "Evaluation of CL 299,263 in the *In Vivo* Micronucleus Assay in Mouse Bone Marrow Cells" (Sharma, R.K.; Genetic Toxicology Lab, American Cyanamid Company, Agricultural Research Division, Princeton, NJ, Study No. 92-18-001, 05/10/93). Fifteen mice/sex/group were dosed with 0, 1250, 2500, and 5000 mg/kg of CL299,263 (Lot # AC6935-63, 98.2% purity, as-is nominal, unadjusted for content of a.i.) orally as a single dose. The test material at dose volume of 20 mL/kg was prepared in corn oil. The micronucleated polychromatic erythrocyte frequency was determined at 24, 48, and 72 hours after administration from 5 mice/sex/group. CL299,263 did not induce micronuclei in male or female mice at any dose at any harvest time. Based on these results, CL299,263 was concluded to be negative for causing cytogenetic damage as evaluated by micronucleus induction. **No adverse effect indicated. Study Acceptable. (Eya, 08/24/00).

SUBCHRONIC STUDIES

(90-day feeding study, dogs)

040; 174805; "90-Day Dietary Toxicity Study With AC 299,263 in Purebred Beagle Dogs" (Kelly, C.M., Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ , Laboratory Project: 92-3122, 2/10/94). 821. AC 299,263 (Lot No. AC 6935-63, purity=98.2%) was admixed to the diet at dose levels of 0 (untreated diet), 1000, 10000, or 40000 ppm (0, 34, 329, and 1333 mg/kg/day, respectively, for males and 0, 36, 381, and 1403 mg/kg/day, for females) and fed to 4 purebred beagle dogs per sex per dose for 90 days. No mortalities occurred. No treatment-related clinical signs were observed. No treatment-related body weight, hematological, or serum chemistry effects were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)=1333 mg/kg/day (40000 ppm) and NOEL (F)=1403 mg/kg/day (40000 ppm) based on no effects at HDT. **Acceptable**. (Corlett, 7/11/00)

(90-day oral gavage study, rats)

039; 174803; "AC 299,263: A 13-Week Dietary Toxicity Study in the Albino Rat" (Fischer, J.E., American Cyanamid Company, Agricultural Research Division, Princeton, NJ, Laboratory Project: Study T-0495, Toxicology Report Number AX92-4, 9/21/92). 821. AC 299,263 (Lot No. AC 6935-63, purity=98.2%) was admixed to the diet at dose levels of 0 (untreated diet), 1000, 10000, or 20000 ppm (0, 76, 785, and 1550 mg/kg/day, respectively, for males and 0, 86, 880, and 1772 mg/kg/day, for females) and fed to 10 CD® rats per sex per dose for 13 consecutive weeks. No mortalities occurred. No treatment-related clinical signs were observed. No treatment-related body weight, hematological, or serum chemistry effects were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)=1550 mg/kg/day (20000 ppm) and NOEL (F)=1772 mg/kg/day (20000 ppm) based on no effects at HDT. **Acceptable**. (Corlett, 7/5/00)

(28-day dermal study, rats)

041; 174806; "A 28-Day Dermal Toxicity Study with AC 299,263 in Rats" (Blaszcak, D.L, Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ , Laboratory Project Study No. 93-2235, 5/11/95). 822. AC 299,263 (Lot No. AC 6935-63, purity=98.2%), moistened with 0.9% saline, was applied to the clipped skin of 5 Sprague-Dawley derived (CD®) rats per sex per dose at dose levels of 0 (sham control), 250, 500, or 1000 mg/kg/day for 6 hours per day, 5 days per week for a period of 28 days using an occlusive wrap. No mortalities occurred. No treatment-related clinical signs or dermal irritation were observed. No treatment-related body weight, hematological, or serum

chemistry effects were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and dermal)=1000 mg/kg/day based on no effects at HDT. **Acceptable**. (Corlett, 7/17/00)

METABOLISM STUDY

Metabolism, Rat

049; 174830; "CL299,263; Metabolism of ^{14}C-CL 299,263 in Rats" (Chiu, T.Y., American Cyanamid Company, Princeton NJ & Battelle, Columbus, OH, Study No.: MET 95-009, 07/07/95). Forty-four Sprague Dawley rats (5/sex/group) were dosed with ^{14}C-CL 299,263 by a single intravenous (iv) dose at 10 mg/kg or a single oral gavage dose according to the following regiments: (1) 10 mg/kg body weight; (2) 14 day preconditioning with 10 mg/kg non-radiolabelled CL 299,263, followed by 10 mg/kg ^{14}C-CL 299,263; or (3) 1000 mg/kg body weight. The elimination patterns of CL 299,263 indicated that the radioactive residue were rapidly cleared from the body (ca. 95%) excreted in urine and recovered within 12 hours after dosing for all dose groups. Approximately, 74-75% of the radioactivity was absorbed via oral administration at 10 mg/kg dose and 74.4-74.5% excreted in urine and 18.7-24.0% in feces. Much higher proportion of the dose was excreted in feces following oral dose (18.7-24.0%) compared to iv injection (1.9-2.7%), most likely due to incomplete absorption. Three components accounted for ca. 99% of the total urinary radioactivity (98.2%, parent; 0.6%, 5-hydroxymethyl-nicotinic acid metabolite; and 0.4%, 5-carboxy-nicotinic acid metabolite) and ca. 89% of the extractable radioactivity in the feces (76.4%, parent; 9.6%, 5-hydroxymethyl-nicotinic acid metabolite; and 2.5%, 5-carboxy-nicotinic acid metabolite). The radioactive residues in the tissues were low ($\leq$ 0.007%), and no ^{14}C-residues were detected in the expired air. **Study Acceptable. (Eya, 09/01/00)